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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,407	SARIS, CHRIS	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-15,17,40-45,49,50 and 64-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13* is/are allowed.

6)☒ Claim(s) *14,15,17,40-45,49,50 and 64-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/21/04, 7/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 13-15, 17, 40-45, 49, 50 and 64-69 are pending in the instant application. Claims 1-12, 16, 18-39, 46-48 and 51-63 have been canceled as requested by Applicant in the Preliminary Amendment filed July 17, 2003.

Priority

2. Applicant is reminded of the following requirement:

In a continuation or divisional application (other than a continued prosecution application filed under 37 CFR 1.53(d)), the first sentence of the specification or application data sheet (37 CFR 1.76) should include a reference to the prior application(s) from which benefit of priority is claimed, and also the status. See 37 CFR 1.78. The status of application 09/612,033 should be updated (now U.S. Patent No. 6,627,199).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 49 and 50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17 and 18 of U.S. Patent No. 6,627,199. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a fusion polypeptide of SEQ ID NO: 8 or 10, wherein the heterologous amino acid sequence is an IgG constant domain or fragment thereof.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.1 Claims 14, 15, 17, 40-45, 49, 50 and 64-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptides of SEQ ID NOS: 8 and 10 and fusion proteins thereof, does not reasonably provide enablement for an ortholog of SEQ ID NOS: 8 or 10, a polypeptide that is at least about 70% identical to the polypeptides of SEQ ID NOS: 8 or 10, amino acid sequences comprising fragments of at least 25 amino acids thereof, allelic variant or splice variant of the amino acid sequence of SEQ ID NOS: 8 or 10, a polypeptide of SEQ ID NO: 8 or 10 with one to twenty conservative amino acid substitutions, insertions or deletions, or combinations thereof, or a polypeptide encoded by a nucleic acid molecule comprising a fragment of at least 16 nucleotides of SEQ ID NOS: 7 or 9, or a polypeptide encoded by a nucleotide sequence which hybridizes under moderately stringent

conditions to the complements of any of the above nucleic acid sequences, or fusion proteins of the above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses two naturally occurring nucleic acid molecules encoding two polypeptides identified as murine tmst2 receptors. The nucleic acid molecule of SEQ ID NO: 7 encodes a full-length protein of SEQ ID NO: 8, which is 198 amino acids in length, and has been identified as a receptor in the Tumor Necrosis Factor Receptor family. The nucleic acid molecule of SEQ ID NO: 9 is a splice variant and encodes a protein of SEQ ID NO: 10, which is a secreted form of the receptor and is 180 amino acids in length. The polypeptides of SEQ ID NOS: 8 and 10 are identical for the first 170 amino acid residues. The specification teaches that the tmst2 receptor binds murine TRAIL specifically (example 9) and that the secreted form (SEQ ID NO: 10) blocked apoptosis in Jurkat cells induced by murine TRAIL protein (example 6). However, the claims encompass variants of these proteins that diverge substantially in structure, and only two proteins, a naturally occurring receptor and its soluble splice variant, which are identical over 94% of the extracellular domain that has the activity of binding murine TRAIL, have been disclosed. Since only the last 10 amino acids of the C-terminal differ in the soluble protein of SEQ ID NO: 10 from that of the full-length protein of SEQ ID NO: 8, the proteins are actually 100% identical in the extracellular region that has TRAIL binding activity. No other allelic or splice variant or homolog or ortholog has been disclosed. The protein closest in the art to the tsmt2 protein of SEQ ID NO: 10 is the protein disclosed in WO98/43998 as 7F4 (see rejection under 35 U.S.C. 102 below), which has the activity of inducing osteoblast cells. The

sequence alignment between tmst2 and 7F demonstrates that the two proteins are 69.9% identical over their entire lengths, and 79.9% identical from amino acids 7-170 of SEQ ID NO: 10. These two proteins are 70% identical yet have different activities. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

The paragraph bridging pages 17-18 of the specification describe an activity of the polypeptide as capable of inducing immune response in a host animal. An immune response can

be elicited by a polypeptide fragment as small as 6 amino acids, so that a polypeptide that differs substantially in amino acid composition and activity could have this immune inducing activity. However, the specification does not teach why one would desire to make such antibodies in a manner commensurate in scope with the claims, i.e., how to use such. Page 16, lines 3-18 defines "tmst2-receptor polypeptide variants' as polypeptides comprising amino acid sequences which contain one or more amino acid sequence substitutions as compared to the polypeptide set forth in SEQ ID NO: 8 or 10. Under this definition, the vast majority of amino acid sequences may be substituted as long as a small fragment remains of SEQ ID NO: 8 or 10 that can elicit an immune response, and there is no limitation that such immune response be specific for the protein of SEQ ID NO: 8 or 10. Also, a polypeptide that is 70% identical to the protein of SEQ ID NO: 8 or 10 may also have areas of identity that elicit an immune response, but do not have to have the TRAIL binding activity of SEQ ID NO: 8 or 10.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

It is acknowledged that the level of skill of those in the art is high. It is not disclosed and not predictable from the limited teachings of the prior art and specification that the polypeptide variants described above invention would retain the TRAIL binding activity of the polypeptide of SEQ ID NO: 8 or 10. The specification does not provide any working examples of any

variants except for the splice variant, and there is limited guidance as to which amino acids, for example, could be substituted or deleted and still retain the TRAIL binding activity. Thus, the specification fails to teach the skilled artisan how to use the claimed polypeptides without resorting to undue experimentation to determine which variants would retain TRAIL binding activity.

For the reasons discussed above, due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples and written description directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

4.2 Claims 14, 15, 17, 40-45, 49, 50 and 64-69 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes a polypeptide sequence consisting of SEQ ID NO: 8 and its splice variant, SEQ ID NO: 10, which are shown to bind TRAIL. However, the claims as written include polypeptides comprising fragments and homologues, encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, that of SEQ ID NO: 8

and it's splice variant, with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated

polypeptide sequence SEQ ID NO: 8 and the splice variant, which are 100% identical over the TRAIL binding domain. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences except for having "an activity" of the polypeptide, which is not clearly defined in the specification. Further, the instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the polypeptides encompassed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 14, 15, 17, 49, 50 and 64-69 are rejected under 35 U.S.C. 102(a) as being anticipated by Kimura et al., WO 98/43998, Oct. 8, 1998.

Claims 14, 15, 17, 49, 50 and 64-69 encompass polypeptide at least 70 % identical to the polypeptide of SEQ ID NO: 8 or 10 or a protein encoded by a nucleotide sequence comprising a fragment of at least about 16 nucleotides of SEQ ID NO: 7 or 9 or a polypeptide fragment of at least about 25 amino acid residues of SEQ ID NO: 8 or 10 or a polypeptide as set forth in SEQ ID NO: 8 or 10 with at least one modification selected from the group consisting of amino acid

substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, and also to a polypeptide encoded by a nucleic acid molecule which hybridizes to the aforementioned nucleic acids under moderate hybridization conditions, wherein the encoded polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 8 or 10, and fusion protein.

Kimura et al. disclose a nucleic acid molecule and encoded protein (SEQ ID NO: 3, pages 29-31) identified as protein 7F4, a receptor protein. The nucleic acid molecule of Kimura is 90.5% identical to nucleotides 81-1539 of SEQ ID NO: 7 and 90.7% identical to nucleotides 81-523 of SEQ ID NO: 9, and encodes a polypeptide that is 75.1% identical to amino acids 7-195 of SEQ ID NO: 8 and 79.9% identical to amino acids 7-170 of SEQ ID NO: 10 (see attached sequence alignments). Since the specification in the paragraph bridging pages 17-18 identifies biologically active tmst2-receptor polypeptides, fragments, variants and derivatives as polypeptides having at least one activity characteristic of tmst2-receptor polypeptide and includes immunogenic fragments capable of inducing in a host animal antibodies directed to the tmst2 fragment, a polypeptide comprising a fragment of at least 6 amino acids of SEQ ID NO: 8 or 10 would have an activity of the polypeptide of SEQ ID NO: 8 or 10. The polypeptide of Kimura et al. meets the limitations of the claims because it is identical to SEQ ID NO: 7 or 9 in at least 16 nucleotides in length, encodes a polypeptide fragment at least 25 amino acids in length of SEQ ID NO: 8 or 10, or encodes a polypeptide as set forth in SEQ ID NO: 8 or 10 with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, or also would hybridize to such nucleic acid molecules under moderate hybridization conditions.

Kimura et al. also disclose fusion proteins (pages 9-10, pBK-RSV, bluescript will make a fusion protein). Therefore, Kimura et al. anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 40-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimura et al., and further in view of Goeddel et al., PN 5,670,319, Sept. 23, 1997.

Claims 40-45 are drawn to the protein in a composition comprising a pharmaceutically acceptable formulation agent which could be a carrier, or a derivative of the protein which could comprise polyethylene glycol.

The teachings of Kimura are summarized above. Because the Kimura reference is in Japanese, it is not known if Kimura specifically teaches if the protein could be in a composition comprising a pharmaceutically acceptable formulation agent which could be a carrier, or a derivative of the protein which could comprise polyethylene glycol.

Goeddel et al. teaches that proteins such as TNF associated factors can be formulated in therapeutic (pharmaceutical) compositions comprising a carrier (column 39, lines 53-66) and modified by covalent attachment of polyethylene glycol (column 33, lines 43-55).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use Kimura's protein, in a composition comprising a carrier, or

modification with polyethylene glycol, as taught by Goeddel et al., in view of Goeddel et al.'s suggestion that it would be desirable to do so, as cited in the patent. The skilled artisan would be motivated to do so for the purpose of therapy, and a polyethylene glycol derived protein would be more stable in vivo. There would be a reasonable expectation of success, since pharmaceutical compositions and polyethylene glycol derived proteins have been made for many years.

Conclusion

7. Claim 13 is allowed.

Claims 14, 15, 17, 40-45, 49, 50 and 64-69 are rejected.

The full-length polypeptides of SEQ ID NOS: 8 and 10 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PRIMARY EXAMINER